Appendix A

Summaries of studies of unilateral thalamic stimulation for essential tremor or Parkinsonian tremor

Appendix B

"MCAC Categories of Effectiveness"

• *Breakthrough technology:* The improvement in health outcomes is so large that the intervention becomes standard of care.

• *Substantially more effective (approved 9/25/02):* The new intervention improves health outcomes by a substantial margin as compared with established services or medical items.

• *More effective:* The new intervention improves health outcomes by a significant, albeit small, margin as compared with established services or medical items.

• *As effective but with advantages:* The intervention has the same effect on health outcomes as established services or medical items but has some advantages (convenience, rapidity of effect, fewer side effects, other advantages) that some patients will prefer.

- *As effective and with no advantages:* The intervention has the same effect on health outcomes as established alternatives but with no advantages.

- *Less effective but with advantages:* Although the intervention is less effective than established alternatives (but more effective than doing nothing), it has some advantages (such as convenience, tolerability).

- *Less effective and with no advantages:* The intervention is less effective than established alternatives (but more effective than doing nothing) and has no significant advantages.

- *Not effective:* The intervention has no effect or has deleterious effects on health outcomes when compared with "doing nothing," (e.g., treatment with placebo or patient management without the use of a diagnostic test).

Appendix C

Additional Medtronic data presented to the MCAC panel

Appendix D

"The AANS/CNS recommend the following General Indications:

1. The procedure may only be performed with FDA-approved devices, systems, and equipment.

2. The patient and caregiver should have an understanding and willingness to comply with anticipated post surgical evaluations and adjustments of medications and stimulator settings.

3. There should be significant deterioration in the quality and functionality of the patient's life prior to considering use of DBS.

The AANS/CNS recommend the following specific indications by target site:

Subthalamic nucleus:

1. Moderate to severe medically intractable Idiopathic Parkinson's disease as diagnosed by a neurologist with experience in movement disorders. The patient should have had the disease for at least three years and have two or more of the four cardinal features (tremor, rigidity, bradykinesia, and postural instability).

2. Motor response complications or medication side effects of levodopa therapy (including motor fluctuations and dyskinesias) despite all reasonable medical therapies and medication adjustments

3. Bilateral implantation needed to avoid additive effects of stimulation and medication which lead to disabling dyskinesia on the stimulated side (if medicated appropriately for non-stimulated side) or akinesia on the non-stimulated side (if under-medicated for the stimulated side).

VIM Thalamus: (uni- or bilateral, dependent on uni- vs. bilateral disease):

1. Moderate to severe medically intractable Essential Tremor, Parkinsonian tremor, or idiopathic postural or intention tremors

Globus Pallidus Interna:

1. Moderate to severe medically intractable Idiopathic Parkinson's disease as diagnosed by a neurologist with experience in movement disorders. Specific patient selection criteria are the same as for "Subthalamic nucleus" above

2. Moderate to severe medically intractable primary dystonia (i.e. DYT-1, Torticollis, writers cramp)

3. Tardive dystonias from psychotropic medications

The AANS/CNS recommend the following contraindications to DBS:

General contraindications for DBS (all targets):

1. Parkinson's plus syndromes: e.g. Olivo-ponto-cerebellar degeneration, Corticobasal degeneration, Shy-Drager syndrome, Multi-system atrophy, Lewy Body Parkinsonism, and others

2. Patients with demand cardiac pacemakers.

3. Patients with cognitive deterioration/dementia (defined clinically by criteria in DSM IV, with a mini-mental Status examination score of less than 22, or by standard neuropsychological tests with score less than 1.5 standard deviations below normal. (i.e. Mathis dementia rating scores of less than 124, FSIQ of less than 70).

Relative contraindications:

1. Structural lesions of the CNS as the etiology of the movement disorder.

2. Psychiatric conditions (Axis –II or III DSM-IV diagnosis).

3. Moderate to severe radiographic atrophy of the cerebral cortex, brainstem, or cerebellum.

The AANS/CNS recommend the following technical criteria for performing DBS:

DBS electrode insertion should be performed using stereotactic or image-guided techniques. Numerous different systems, both framed and frameless, are available for stereotactic targeting. DBS procedures should only be performed by neurosurgeons skilled in the techniques of stereotactic and functional surgery, who have been trained in the performance of DBS procedures and who have been credentialed by their institutions as competent to perform these procedures. The use of microelectrode recording or macroelectrode stimulation are considered clinically accepted methods for physiological confirmation of the target site. In cases where microelectrode recording

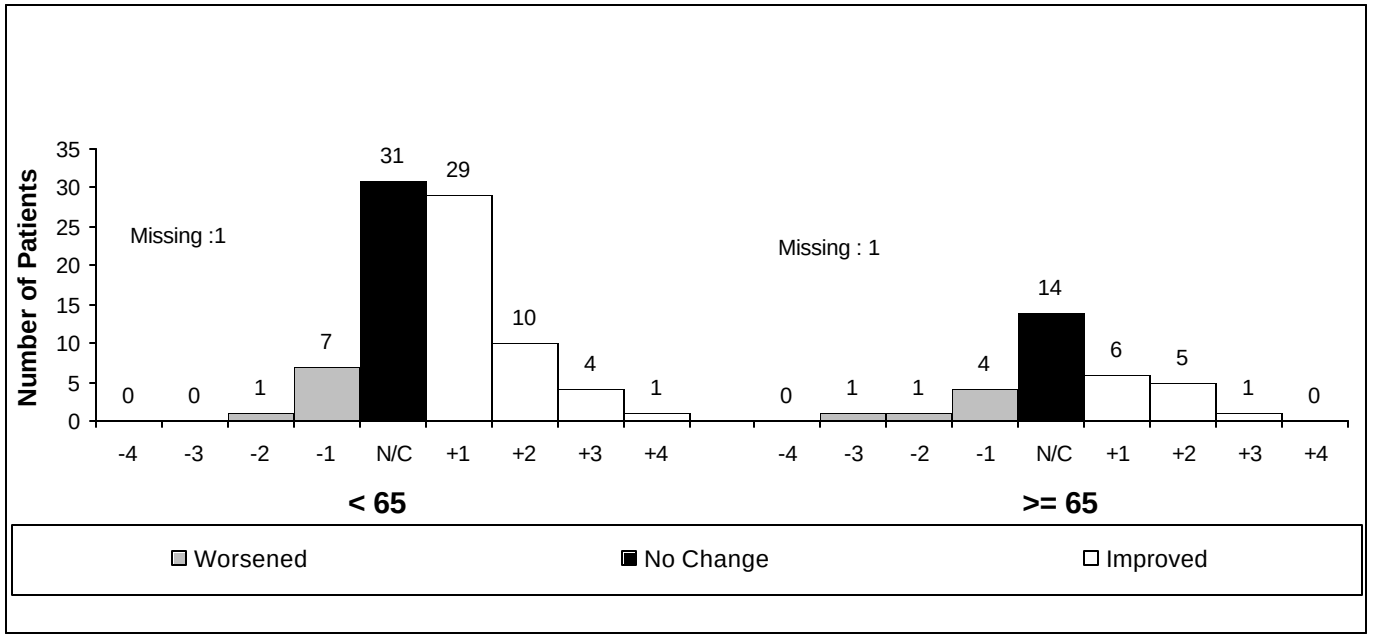
is performed, the assistance of a neurologist or neurophysiologist may help to facilitate decisions on a final target and optimize outcomes. However, an appropriately trained neurosurgeon who is skilled in the performance and interpretation of microelectrode recording may not require intraoperative assistance in this area. Interpretation of intraoperative neurophysiological data can thus be performed either by a qualified neurologist or neurosurgeon.

It has been recommended that centers performing DBS should be equipped for functional stereotactic procedures, with the availability of high-resolution scanners, navigational equipment, and electrophysiological monitoring equipment. Optimal outcomes can be achieved by physicians well experienced in the pathology and treatment of movement disorders, stereotactic neurosurgery, and electrophysiology."

Additional Medtronic Data Presented to the MCAC Panel

Note: Please refer to the Food and Drug Administration (FDA) Summary of Safety and Effectiveness document at http://www.fda.gov/cdrh/pdf/p960009s7.html for complete information and data description related to the following data.

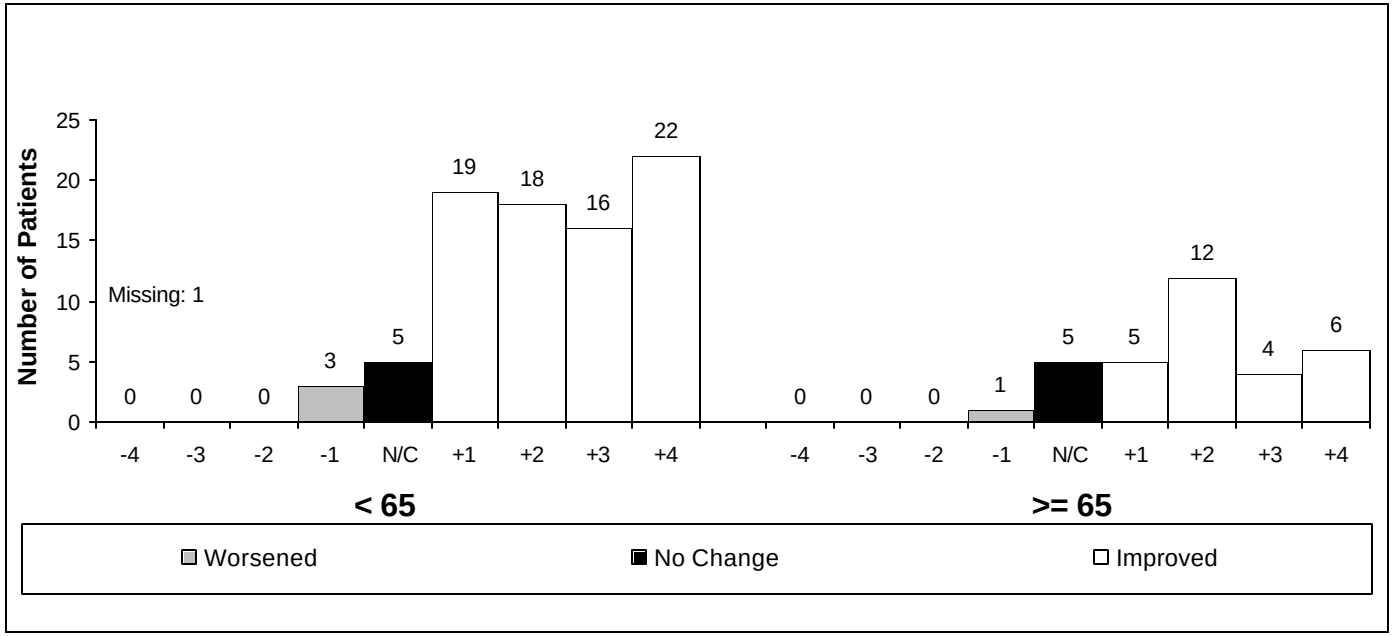
Figure 1 Absolute change in UPDRS TME scores while ON medication by age strata*: pre-implant to 12 months



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
TME Score Change	> 35	>25 and ≤ 35	>15 and ≤ 25	>5 and ≤ 15	>-5 and ≤ 5	>-15 and ≤ -5	>-25 and ≤ -15	>-35 and ≤ -25	≤ -35

*Data presented include 84 of 116 patients with age< 65 and 33 of 44 patients with age>= 65 who had verifiable source documentation for this efficacy measure.

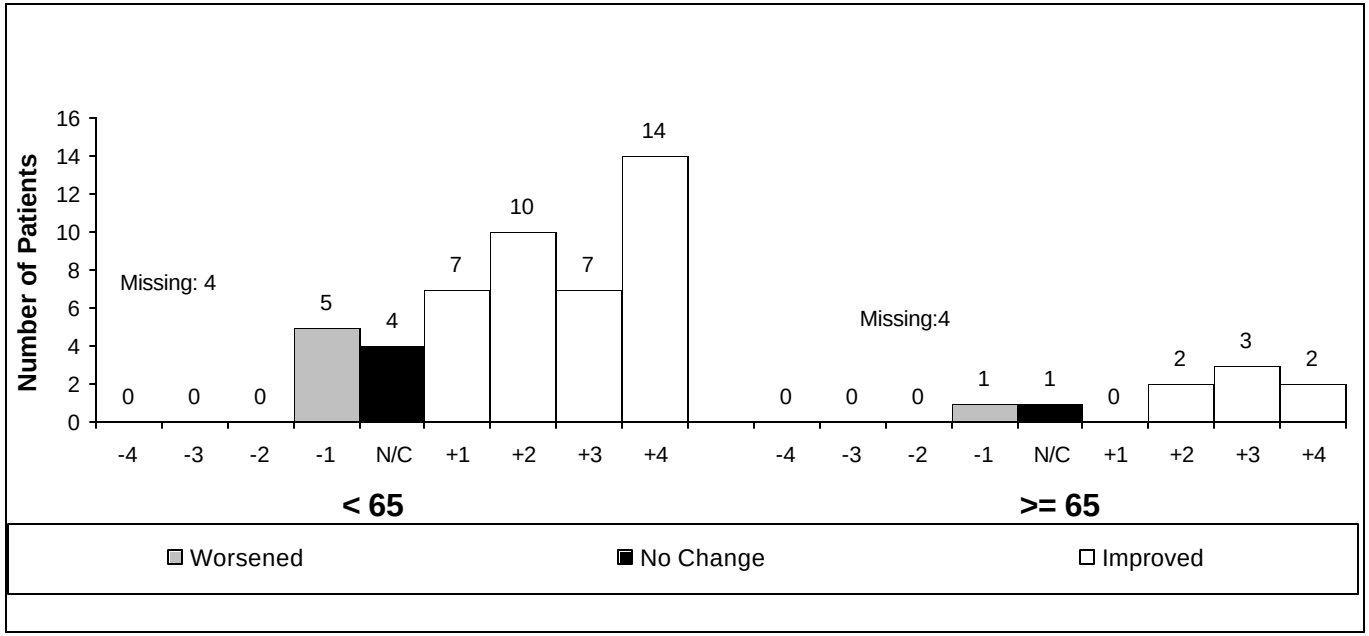
Figure 2 **Absolute change in UPDRS TME scores while OFF medication by age strata*: pre-implant to 12 months**



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
TME Score Change	> 35	>25 and ≤ 35	>15 and ≤ 25	>5 and ≤ 15	>-5 and ≤ 5	>-15 and ≤ -5	>-25 and ≤ -15	>-35 and ≤ -25	≤ -35

*Data presented include 84 of 116 patients with age< 65 and 33 of 44 patients with age>= 65 who had verifiable source documentation for this efficacy measure.

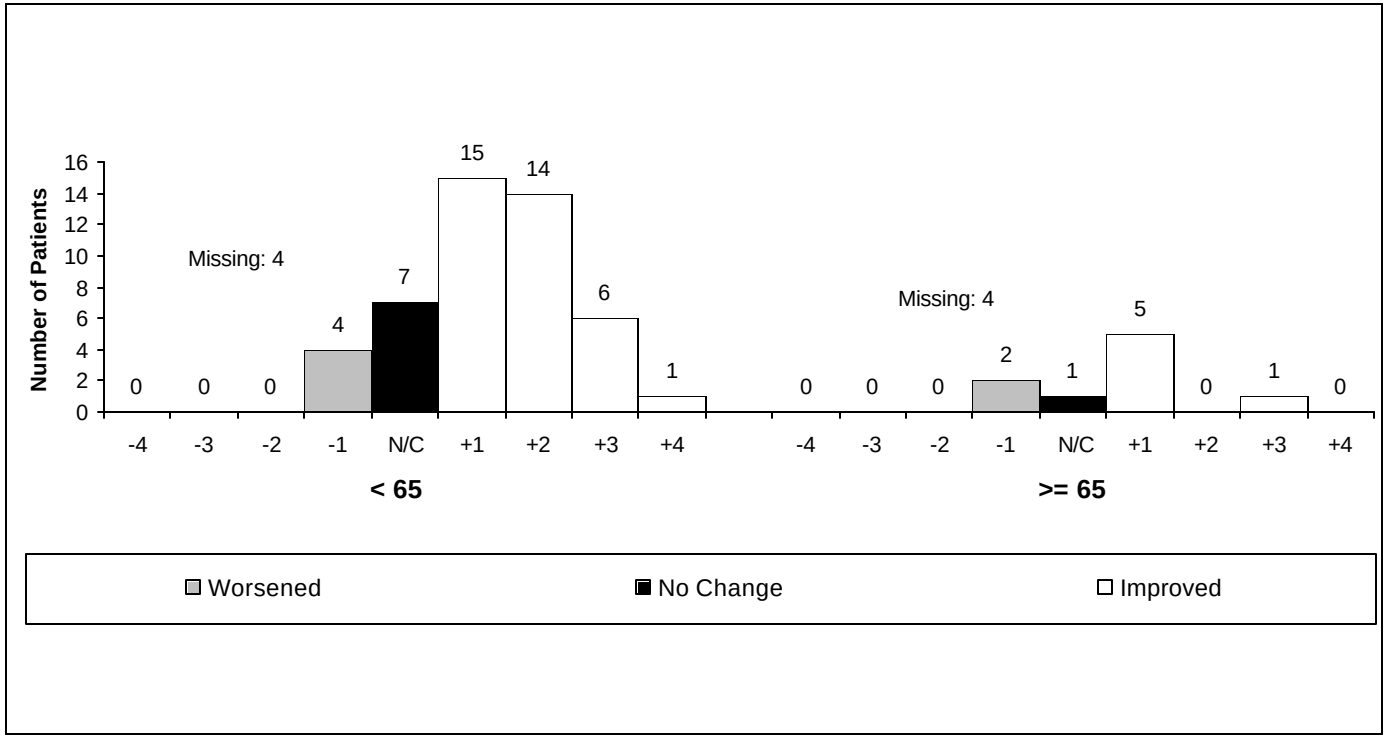
Figure 3 Absolute change in "on" time by age strata*: pre -implant to 12 months



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in ON Time: hours	≤ -10	≤ -7 and > -10	≤ -4 and > -7	≤ -1 and > -4	> -1 and < 1	≥ 1 and < 4	≥ 4 and < 7	≥ 7 and < 10	≥ 10

*Data presented include 51 of 116 patients with age< 65 and 13 of 44 patients with age>= 65 who had verifiable source documentation for this efficacy measure.

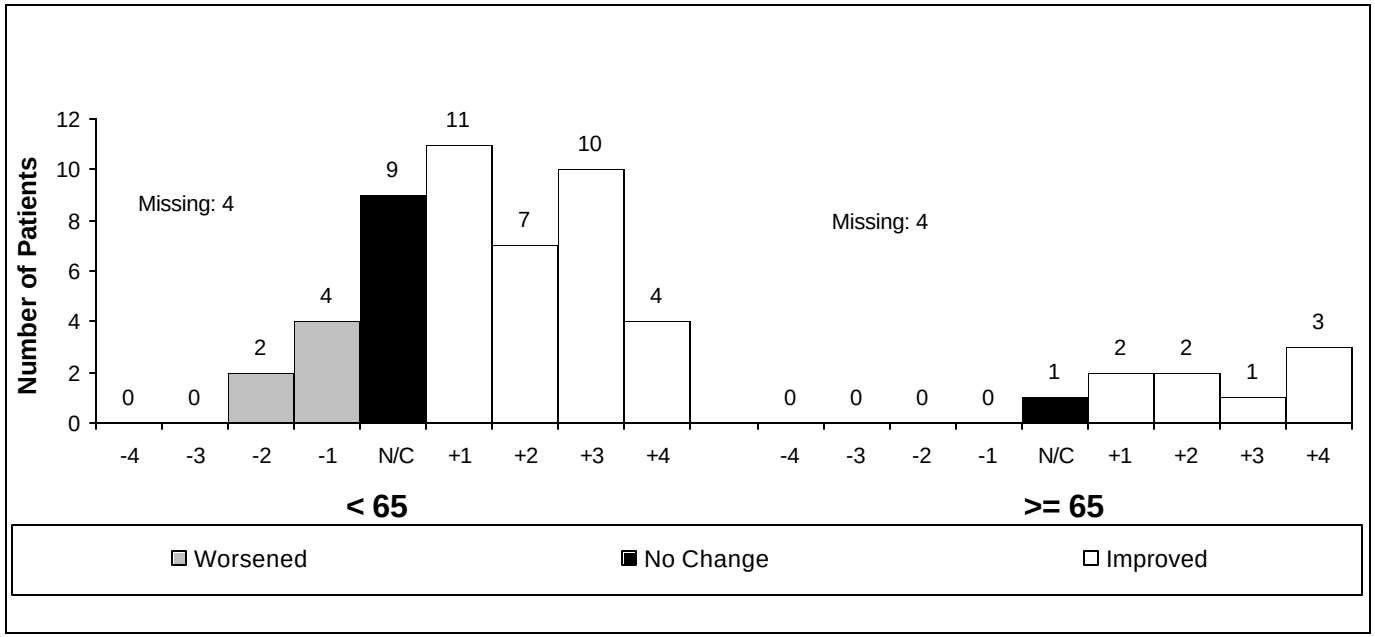
Figure 4 Absolute change in "on" time with dyskinesia by age strata* : pre-implant to 12 months



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in ON w/ Dysk Time	≥ 10	≥ 7 and < 10	≥ 4 and < 7	≥ 1 and < 4	< 1 and > -1	≤ -1 and > -4	≤ -4 and > -7	≤ -7 and > -10	≤ -10

*Data presented include 51 of 116 patients with age< 65 and 13 of 44 patients with age>= 65 who had verifiable source documentation for this efficacy measure.

Figure 5 Absolute change in "off" time by age strata*: pre-implant to 12 months



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in OFF Time	≥ 10	≥ 7 and < 10	≥ 4 and < 7	≥ 1 and < 4	< 1 and > -1	≤ -1 and > -4	≤ -4 and > -7	≤ -7 and > -10	≤ -10

*Data presented include 51 of 116 patients with age< 65 and 13 of 44 patients with age>= 65 who had verifiable source documentation for this efficacy measure.

Table 1. Absolute change in UPDRS TME scores while ON Medication by center: pre-implant to 12 months

	Number of Patients in each Range of Score Change Category [3]												
Center	**-4**	**-3**	**-2**	**-1**	**NC**	**+1**	**+2**	**+3**	**+4**	**Total Patients Enrolled**	**Total Patients with source verifiable data [1]**	**# of Patients Improved [2]**	**% of Patients Improved**
Center 11	0	0	0	4	7	2	3	1	0	20	17	6	35.3
Center 17	0	0	0	1	7	4	1	0	0	18	13	5	38.5
Center 6	0	0	0	1	4	6	0	0	0	15	11	6	54.5
Center 14	0	0	0	0	4	3	1	2	0	15	10	6	60.0
Center 10	0	0	0	1	2	3	2	2	1	12	11	8	72.7
Center 5	0	0	0	0	2	5	3	0	0	12	10	8	80.0
Center 7	0	0	1	0	3	2	0	0	0	10	6	2	33.3
Center 3	0	0	0	0	6	2	0	0	0	8	8	2	25.0
Center 12	0	0	0	1	4	0	0	0	0	7	5	0	0.0
Center 15	0	0	0	1	1	1	3	0	0	6	6	4	66.7
Center 1	0	0	1	1	2	1	0	0	0	6	5	1	20.0
Center 8	0	0	0	1	0	3	1	0	0	6	5	4	80.0
Center 16	0	0	0	0	2	1	1	0	0	4	4	2	50.0
Center 13	0	0	0	0	0	2	0	0	0	3	2	2	100.0
Center 4	0	1	0	0	1	0	0	0	0	3	2	0	0.0
Center 2	0	0	0	0	0	0	0	0	0	1	0	0	0.0

(1) Data presented include 117 of 160 patients who had verifiable source documentation for this efficacy measure. Two of 117 patients had missing data at 12 months: center 2 had missing data for 1 patient and center 14 had missing data for 1 patient.

(2) Patients in +1 to +4 Category.

(3)

Definition of Range of Score Change Categories									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
TME Score Change	> 35	>25 and ≤ 35	>15 and ≤ 25	>5 and ≤ 15	>-5 and ≤ 5	>-15 and ≤ -5	>-25 and ≤ -15	>-35 and ≤ -25	≤ -35

Table 2. Absolute change in UPDRS TME scores while OFF Medication by center: pre-implant to 12 months

	Number of Patients in each Range of Score Change Category [3]												
Center	**-4**	**-3**	**-2**	**-1**	**NC**	**+1**	**+2**	**+3**	**+4**	**Total Patients Enrolled**	**Total Patients with source verifiable data [1]**	**# of Patients Improved [2]**	**% of Patients Improved**
Center 11	0	0	0	1	0	5	6	1	4	20	17	16	94.1
Center 17	0	0	0	0	0	2	3	6	2	18	13	13	100.0
Center 6	0	0	0	0	1	1	3	1	5	15	11	10	90.9
Center 14	0	0	0	1	5	2	0	1	1	15	10	4	40.0
Center 5	0	0	0	0	0	0	1	2	7	12	10	10	100.0
Center 10	0	0	0	0	1	3	4	2	1	12	11	10	90.9
Center 7	0	0	0	0	0	2	1	1	2	10	6	6	100.0
Center 3	0	0	0	0	0	1	4	3	0	8	8	8	100.0
Center 12	0	0	0	0	1	3	1	0	0	7	5	4	80.0
Center 1	0	0	0	1	1	1	2	0	0	6	5	3	60.0
Center 8	0	0	0	0	0	1	0	0	4	6	5	5	100.0
Center 15	0	0	0	0	1	1	2	1	1	6	6	5	83.3
Center 16	0	0	0	0	0	2	1	1	0	4	4	4	100.0
Center 4	0	0	0	1	0	0	0	1	0	3	2	1	50.0
Center 13	0	0	0	0	0	0	2	0	0	3	2	2	100.0
Center 2	0	0	0	0	0	0	0	0	1	1	1	1	100.0

(1) Data presented include 117 of 160 patients who had verifiable source documentation for this efficacy measure. One of 117 patients had missing data at 12 months: center 14 had missing data for 1 patient.

(2) Patients in +1 to +4 Category.

(3)

Definition of Range of Score Change Categories									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
TME Score Change	> 35	>25 and ≤ 35	>15 and ≤ 25	>5 and ≤ 15	>-5 and ≤ 5	>-15 and ≤ -5	>-25 and ≤ -15	>-35 and ≤ -25	≤ -35

Table 3. Absolute change in “on” time by center: pre-implant to 12 months

	Number of patients in each “on” Time Range [3]												
Center	**-4**	**-3**	**-2**	**-1**	**NC**	**+1**	**+2**	**+3**	**+4**	**Total Patients Enrolled**	**Total Patients with source verifiable data [1]**	**# of Patients Improved [2]**	**% of Patients Improved**
Center 11	0	0	0	1	0	1	5	1	3	20	11	10	90.9
Center 6	0	0	0	1	0	0	1	2	3	15	7	6	85.7
Center 14	0	0	0	0	0	1	1	1	1	15	4	4	100.0
Center 5	0	0	0	0	0	0	0	0	1	12	1	1	100.0
Center 10	0	0	0	1	0	2	2	1	1	12	7	6	85.7
Center 7	0	0	0	1	1	1	0	0	4	10	7	5	71.4
Center 3	0	0	0	0	0	0	0	3	1	8	4	4	100.0
Center 12	0	0	0	1	1	0	1	0	0	7	3	1	33.3
Center 1	0	0	0	0	1	2	0	1	0	6	4	3	75.0
Center 8	0	0	0	0	1	0	1	1	0	6	3	2	66.7
Center 9	0	0	0	0	0	0	1	0	0	5	1	1	100.0
Center 4	0	0	0	0	1	0	0	0	0	3	1	0	0.0
Center 13	0	0	0	1	0	0	0	0	1	3	2	1	50.0
Center 2	0	0	0	0	0	0	0	0	1	1	1	1	100.0

(1) Data presented include 64 of 160 patients who had verifiable source documentation for this efficacy measure. Eight of 64 patients had incomplete data at baseline or 12 months: center 1 had incomplete data for 1 patient; center 6 and center 11 each had incomplete data for 2 patients; center 14 had incomplete data for 3 patients.

(2) Patients in +1 to +4 Category.

(3)

Definition of “on” Time Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in “on” Time: hours	≤ -10	≤ -7 and > -10	≤ -4 and > -7	≤ -1 and > -4	> -1 and < 1	≥ 1 and < 4	≥ 4 and < 7	≥ 7 and < 10	≥ 10

Table 4. Absolute change in “on” time with dyskinesia by center: pre-implant to 12 months

	Number of patients in each “on” Time with Dyskinesia Range [3]												
Center	**-4**	**-3**	**-2**	**-1**	**NC**	**+1**	**+2**	**+3**	**+4**	**Total Patients Enrolled**	**Total Patients with source verifiable data [1]**	**# of Patients Improved [2]**	**% of Patients Improved**
Center 11	0	0	0	1	0	5	4	1	0	20	11	10	90.9
Center 6	0	0	0	0	1	5	0	1	0	15	7	6	85.7
Center 14	0	0	0	0	2	1	1	0	0	15	4	2	50.0
Cener 5	0	0	0	0	0	0	1	0	0	12	1	1	100.0
Center 10	0	0	0	1	0	3	2	1	0	12	7	6	85.7
Center 7	0	0	0	1	1	2	2	1	0	10	7	5	71.4
Center 3	0	0	0	0	0	1	2	1	0	8	4	4	100.0
Center 12	0	0	0	1	0	2	0	0	0	7	3	2	66.7
Center 1	0	0	0	1	1	1	1	0	0	6	4	2	50.0
Center 8	0	0	0	0	1	0	0	1	1	6	3	2	66.7
Center 9	0	0	0	0	0	0	0	1	0	5	1	1	100.0
Center 4	0	0	0	1	0	0	0	0	0	3	1	0	0.0
Center 13	0	0	0	0	2	0	0	0	0	3	2	0	0.0
Center 2	0	0	0	0	0	0	1	0	0	1	1	1	100.0

(1) Data presented include 64 of 160 patients who had verifiable source documentation for this efficacy measure. Eight of 64 patients had incomplete data at baseline or 12 months: center 1 had incomplete data for 1 patient; center 6 and center 11 each had incomplete data for 2 patients; center 14 had incomplete data for 3 patients.

(2) Patients in +1 to +4 Category.

(3)

Definition of “on” Time with Dyskinesia Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in “on” w/ Dysk Time: hours	≥ 10	≥ 7 and < 10	≥ 4 and < 7	≥ 1 and < 4	< 1 and > -1	≤ -1 and > -4	≤ -4 and > -7	≤ -7 and > -10	≤ -10

Table 5. Absolute change in "off" time by center: pre-implant to 12 months

	Number of patients in each "off" Time Range [3]												
Center	**-4**	**-3**	**-2**	**-1**	**NC**	**+1**	**+2**	**+3**	**+4**	**Total Patients Enrolled**	**Total Patients with source verifiable data [1]**	**# of Patients Improved [2]**	**% of Patients Improved**
Center 11	0	0	0	1	2	3	1	2	2	20	11	8	72.7
Center 6	0	0	0	0	0	2	1	3	1	15	7	7	100.0
Center 14	0	0	0	0	1	0	0	1	2	15	4	3	75.0
Center 5	0	0	0	0	0	0	0	1	0	12	1	1	100.0
Center 10	0	0	1	1	1	2	2	0	0	12	7	4	57.1
Center 7	0	0	0	1	1	2	0	2	1	10	7	5	71.4
Center 3	0	0	0	0	0	2	1	1	0	8	4	4	100.0
Center 12	0	0	0	0	2	1	0	0	0	7	3	1	33.3
Center 1	0	0	0	0	2	1	1	0	0	6	4	2	50.0
Center 8	0	0	0	1	1	0	1	0	0	6	3	1	33.3
Center 9	0	0	1	0	0	0	0	0	0	5	1	0	0.0
Center 4	0	0	0	0	0	0	1	0	0	3	1	1	100.0
Center 13	0	0	0	0	0	0	1	1	0	3	2	2	100.0
Center 2	0	0	0	0	0	0	0	0	1	1	1	1	100.0

(1) Data presented include 64 of 160 patients who had verifiable source documentation for this efficacy source. Eight of 64 patients had incomplete data at baseline or 12 months: center 1 had incomplete data for 1 patient; center 6 and center 11 each had incomplete data for 2 patients; center 14 had incomplete data for 3 patients.

(2) Patients in +1 to +4 Category.

(3)

Definition of "off" Time Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in "off" Time: hours	≥ 10	≥ 7 and < 10	≥ 4 and < 7	≥ 1 and < 4	< 1 and > -1	≤ -1 and > -4	≤ -4 and > -7	≤ -7 and > -10	≤ -10

Summary of Adverse Events by Age for All Patients Reported in the Parkinson's Disease Clinical Trial

	Age < 65 (n=116)				Age >=65 (n=44)				
Major Category	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI ****	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI ****	**P-value ****
Cardiovascular*	32 (4)	9	16 (13.8)	7.5, 20.1	32 (10)	15	16 (36.4)	22.1, 50.6	<.01
Cerebral Spinal Fluid Abnormality	1 (0)	1	1 (0.9)	0.0, 2.5	4 (1)	4	4 (9.1)	0.6, 17.6	.02
Cognitive									
Alteration Of Mentation*	8 (1)	3	8 (6.9)	2.3, 11.5	8 (4)	6	6 (13.6)	3.5, 23.8	NS
Amnesia*	3 (0)	1	3 (2.6)	0.0, 5.5	6 (2)	5	5 (11.4)	2.0, 20.7	.04
Confusion*	26 (1)	12	25 (21.6)	14.1, 29	30 (4)	15	19 (43.2)	28.5, 57.8	<.01
Delusions*	5 (4)	0	4 (3.4)	0.1, 6.8	0 (0)	0	0 (0)	0.0, 8.0	NS
Dementia	0 (0)	0	0 (0.0)	0.0, 3.1	2 (0)	2	2 (4.5)	0.0, 10.7	NS
Hallucinations	6 (1)	0	5 (4.3)	0.6, 8.0	9 (1)	1	6 (13.6)	3.5, 23.8	NS
Thinking Abnormal*	23 (2)	9	21 (18.1)	11.1, 25.1	16 (1)	7	12 (27.3)	14.1, 40.4	NS
Cognitive Total*	71 (9)	25	47 (40.5)	31.6, 49.5	71 (12)	36	25 (56.8)	42.2, 71.5	NS
Convulsions	6 (6)	5	6 (5.2)	1.1, 9.2	1 (0)	0	1 (2.3)	0.0, 6.7	NS
Dbs System									
External*	5 (0)	4	4 (3.4)	0.1, 6.8	2 (0)	2	2 (4.5)	0.0, 10.7	NS
Internal*	63 (27)	54	40 (34.5)	25.8, 43.1	23 (6)	20	15 (34.1)	20.1, 48.1	NS
Dbs System Total*	68 (27)	58	41 (35.3)	26.6, 44.0	25 (6)	22	16 (36.4)	22.1, 50.6	NS
Death	2 (2)	0	2 (1.7)	0.0, 4.1	1 (1)	0	1 (2.3)	0.0, 6.7	NS
Depression*	36 (10)	3	30 (25.9)	17.9, 33.8	5 (0)	1	5 (11.4)	2, 20.7	<.05
Eye									
Eye Disorder*	8 (0)	3	7 (6.0)	1.7, 10.4	2 (0)	2	2 (4.5)	0.0, 10.7	NS
Eye Infection	2 (0)	0	2 (1.7)	0.0, 4.1	3 (0)	0	2 (4.5)	0.0, 10.7	NS
Visual Disturbances*	21 (4)	14	21 (18.1)	11.1, 25.1	12 (2)	6	9 (20.5)	8.5, 32.4	NS
Eye Total*	31 (4)	17	27 (23.3)	15.6, 31.0	17 (2)	8	12 (27.3)	14.1, 40.4	NS
General									
Ear	3 (0)	0	3 (2.6)	0.0, 5.5	1 (0)	0	1 (2.3)	0.0, 6.7	NS
Gastrointestinal*	35 (3)	5	29 (25.0)	17.1, 32.9	20 (2)	4	12 (27.3)	14.1, 40.4	NS
Metabolic/Nutritional*	27 (2)	4	23 (19.8)	12.6, 27.1	9 (2)	2	6 (13.6)	3.5, 23.8	NS
Musculo-Skeletal*	16 (6)	1	14 (12.1)	6.1, 18.0	5 (1)	1	5 (11.4)	2.0, 20.7	NS
Respiratory	31 (8)	4	21 (18.1)	11.1, 25.1	12 (2)	4	9 (20.5)	8.5, 32.4	NS
Skin And Appendages									
Ecchymosis	0	0	0 (0)	0.0,3.1	1 (0)	0	1 (2.3)	0.0, 6.7	NS
Erosion*	2 (2)	1	2 (1.7)	0.0, 4.1	1 (1)	1	1 (2.3)	0.0, 6.7	NS

	Age < 65 (n=116)				Age >=65 (n=44)				
Major Category	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI ****	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI ****	**P-value ****
Infection, fungal	2 (0)	0	2 (1.7)	0.0, 4.1	0 (0)	0	0 (0.0)	0.0, 8.0	NS
Petechia	1 (0)	0	1 (0.9)	0.0, 2.5	0 (0)	0	0 (0.0)	0.0, 8.0	NS
Psoriasis	1 (1)	0	1 (0.9)	0.0, 2.5	0 (0)	0	0 (0.0)	0.0, 8.0	NS
Lymphedema	0 (0)	0	0 (0.0)	0.0, 3.1	1 (0)	0	1 (2.3)	0.0, 6.7	NS
Rash	6 (0)	0	6 (5.2)	1.1, 9.2	1 (0)	0	1 (2.3)	0.0, 6.7	NS
Skin Disorder	4 (0)	0	4 (3.4)	0.1, 6.8	2 (1)	2	2 (4.5)	0.0, 10.7	NS
Sweating*	2 (0)	1	2 (1.7)	0.0, 4.1	1 (0)	0	1 (2.3)	0.0, 6.7	NS
Skin And Appendages Total*	18 (3)	2	16 (13.8)	7.5, 20.1	7 (2)	3	6 (13.6)	3.5, 23.8	NS
Systemic*	41 (6)	2	29 (25.0)	17.1, 32.9	34 (8)	5	20 (45.5)	30.7, 60.2	.01
Urogenital*	31 (1)	2	26 (22.4)	14.8, 30.0	22 (6)	1	17 (38.6)	24.2, 53.0	.04
General Total*	202 (29)	20	75 (64.7)	56.0, 73.4	110 (23)	20	35 (79.5)	67.6, 91.5	NS
Paresis/Asthenia*	7 (0)	1	7 (6.0)	1.7, 10.4	9 (1)	5	9 (20.5)	8.5, 32.4	.01
Hemiplegia/Hemiparesis*	5 (2)	3	5 (4.3)	0.6, 8.0	10 (6)	7	8 (18.2)	6.8, 29.6	<.01
Device-Related Infection									NS
Infection With Explant*	13 (13)	13	8 (6.9)	2.3, 11.5	2 (2)	2	1 (2.3)	0.0, 6.7	NS
Infection Without Explant*	15 (8)	14	10 (8.6)	3.5, 13.7	2 (0)	2	2 (4.5)	0.0, 10.7	NS
Device-Related Infection Total*	28 (21)	27	14 (12.1)	6.1, 18.0	4 (2)	4	3 (6.8)	0.0, 14.3	NS
Intracranial Hemorrhage*	5 (3)	5	4 (3.4)	0.1, 6.8	8 (5)	8	8 (18.2)	6.8, 29.6	<.01
Neuropsychological									
Anxiety*	20 (5)	1	16 (13.8)	7.5, 20.1	5 (2)	1	4 (9.1)	0.6, 17.6	NS
Apathy	4 (2)	0	4 (3.4)	0.1, 6.8	0 (0)	0	0 (0.0)	0.0, 8.0	NS
Psychiatric Disturbances									
Hostility	4 (2)	0	3 (2.6)	0.0, 5.5	2 (0)	0	2 (4.5)	0.0, 10.7	NS
Paranoid Reaction	0 (0)	0	0 (0.0)	0.0, 3.1	1 (0)	0	1 (2.3)	0.0, 6.7	NS
Manic Reaction*	5 (2)	2	3 (2.6)	0.0, 5.5	0 (0)	0	0 (0.0)	0.0, 8.0	NS
Neurosis*	1 (0)	1	1 (0.9)	0.0, 2.5	0 (0)	0	0 (0.0)	0.0, 8.0	NS
Personality disorder	10 (4)	0	7 (6.0)	1.7, 10.4	2 (0)	1	2 (4.5)	0.0, 10.7	NS
Psychiatric Disturbances Total*	20 (8)	3	11 (9.5)	4.2, 14.8	5 (0)	1	3 (6.8)	0.0, 14.3	NS
Suicide Attempt	0 (0)	0	0 (0.0)	0.0, 3.1	1 (1)	0	1 (2.3)	0.0, 6.7	NS
Neuropsychological Total*	44 (15)	4	25 (21.6)	14.1, 29.0	11 (3)	2	6 (13.6)	3.5, 23.8	NS
Sensory Impairment									
Headache*	13 (4)	6	11 (9.5)	4.2, 14.8	3 (0)	2	3 (6.8)	0.0, 14.3	NS
Hearing*	2 (0)	1	2 (1.7)	0.0, 4.1	0 (0)	0	0 (0)	0.0, 8.0	NS
Neuralgia	2 (1)	0	2 (1.7)	0.0, 4.1	1 (1)	0	1 (2.3)	0.0, 6.7	NS

	Age < 65 (n=116)				Age >=65 (n=44)				
Major Category	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI ****	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI ****	**P-value ****
Neuropathy	0 (0)	0	0 (0.0)	0.0, 3.1	1 (0)	1	1 (2.3)	0.0, 6.7	NS
Pain*	51 (3)	10	37 (31.9)	23.4, 40.4	20 (2)	5	13 (29.5)	16.1, 43.0	NS
Paresthesia*	32 (1)	21	24 (20.7)	13.3, 28.1	5 (0)	2	5 (11.4)	2.0, 20.7	NS
Sensory Disturbance*	13 (1)	8	11 (9.5)	4.2, 14.8	5 (1)	3	5 (11.4)	2.0, 20.7	NS
Sensory Impairment Total*	113 (10)	46	61 (52.6)	43.5, 61.7	35 (4)	13	18 (40.9)	26.4, 55.4	NS
Sleep*	30 (1)	5	26 (22.4)	14.8, 30.0	15 (0)	3	11 (25)	12.2, 37.8	NS
Speech/Language									
Dysarthria*	34 (2)	23	30 (25.9)	17.9, 33.8	13 (4)	9	12 (27.3)	14.1, 40.4	NS
Speech/Language*	20 (7)	9	14 (12.1)	6.1, 18.0	10 (2)	7	9 (20.5)	8.5, 32.4	NS
Speech/Language Total*	54 (9)	32	42 (36.2)	27.5, 45.0	23 (6)	16	17 (38.6)	24.2, 53.0	NS
Subcutaneous Hemorrhage/Seroma*	9 (4)	6	9 (7.8)	2.9, 12.6	6 (2)	4	5 (11.4)	2.0, 20.7	NS
Worsening Of Motor Impairment/PD Symptom									
Abnormal Gait*	25 (1)	7	19 (16.4)	9.6, 23.1	13 (3)	3	11 (25)	12.2, 37.8	NS
Akinesia/Bradykinesia*	15 (0)	6	14 (12.1)	6.1, 18.0	5 (0)	3	5 (11.4)	2.0, 20.7	NS
Therapeutic Response, decreased	1 (0)	0	1 (0.9)	0.0, 2.5	0 (0)	0	0 (0.0)	0.0, 8.0	NS
Dyskinesia*	107 (20)	52	48 (41.4)	32.4, 50.3	24 (2)	12	12 (27.3)	14.1, 40.4	NS
Dysphagia*	6 (1)	1	6 (5.2)	1.1, 9.2	7 (2)	1	6 (13.6)	3.5, 23.8	NS
Incoordination*	25 (3)	10	21 (18.1)	11.1, 25.1	8 (0)	4	8 (18.2)	6.8, 29.6	NS
Myoclonus	1 (0)	1	1 (0.9)	0.0, 2.5	0 (0)	0	0 (0.0)	0.0,8.0	NS
Rigidity*	12 (1)	2	11 (9.5)	4.2, 14.8	1 (0)	1	1 (2.3)	0.0, 6.7	NS
Tremor*	17 (0)	3	14 (12.1)	6.1, 18.0	5 (0)	1	4 (9.1)	0.6, 17.6	NS
Worse Motor Fluctuations*	68 (9)	15	44 (37.9)	29.1, 46.8	17 (6)	8	12 (27.3)	14.1, 40.4	NS
Worsening Of Motor Impairment/PD Symptom Total*	277 (35)	97	83 (71.6)	63.3, 79.8	80 (13)	33	27 (61.4)	47.0, 75.8	NS

* *Includes adverse events related to the system components.*

** Note: Exact 95% confidence intervals were used when the # (%) of patients was 0 (0%) because the normal approximation to the binomial does not provide a confidence interval. In every other case, the normal approximation to the binomial was used to calculate confidence intervals. P-values for the comparison of percent of patients with the event between age groups are based on the chi square test unless any expected value is less than 5, in which case Fisher's exact test was used. NS denotes not statistically significant at the .05 level.

Appendix D

"The AANS/CNS recommend the following General Indications:

1. The procedure may only be performed with FDA-approved devices, systems, and equipment.

2. The patient and caregiver should have an understanding and willingness to comply with anticipated post surgical evaluations and adjustments of medications and stimulator settings.

3. There should be significant deterioration in the quality and functionality of the patient's life prior to considering use of DBS.

The AANS/CNS recommend the following specific indications by target site:

Subthalamic nucleus:

1. Moderate to severe medically intractable Idiopathic Parkinson's disease as diagnosed by a neurologist with experience in movement disorders. The patient should have had the disease for at least three years and have two or more of the four cardinal features (tremor, rigidity, bradykinesia, and postural instability).

2. Motor response complications or medication side effects of levodopa therapy (including motor fluctuations and dyskinesias) despite all reasonable medical therapies and medication adjustments

3. Bilateral implantation needed to avoid additive effects of stimulation and medication which lead to disabling dyskinesia on the stimulated side (if medicated appropriately for non-stimulated side) or akinesia on the non-stimulated side (if under-medicated for the stimulated side).

VIM Thalamus: (uni- or bilateral, dependent on uni- vs. bilateral disease):

1. Moderate to severe medically intractable Essential Tremor, Parkinsonian tremor, or idiopathic postural or intention tremors

Globus Pallidus Interna:

1. Moderate to severe medically intractable Idiopathic Parkinson's disease as diagnosed by a neurologist with experience in movement disorders. Specific patient selection criteria are the same as for "Subthalamic nucleus" above

2. Moderate to severe medically intractable primary dystonia (i.e. DYT-1, Torticollis, writers cramp)

3. Tardive dystonias from psychotropic medications

The AANS/CNS recommend the following contraindications to DBS:

General contraindications for DBS (all targets):

1. Parkinson's plus syndromes: e.g. Olivo-ponto-cerebellar degeneration, Corticobasal degeneration, Shy-Drager syndrome, Multi-system atrophy, Lewy Body Parkinsonism, and others

2. Patients with demand cardiac pacemakers.

3. Patients with cognitive deterioration/dementia (defined clinically by criteria in DSM IV, with a mini-mental Status examination score of less than 22, or by standard neuropsychological tests with score less than 1.5 standard deviations below normal. (i.e. Mathis dementia rating scores of less than 124, FSIQ of less than 70).

Relative contraindications:

1. Structural lesions of the CNS as the etiology of the movement disorder.

2. Psychiatric conditions (Axis –II or III DSM-IV diagnosis).

3. Moderate to severe radiographic atrophy of the cerebral cortex, brainstem, or cerebellum.

The AANS/CNS recommend the following technical criteria for performing DBS:

DBS electrode insertion should be performed using stereotactic or image-guided techniques. Numerous different systems, both framed and frameless, are available for stereotactic targeting. DBS procedures should only be performed by neurosurgeons skilled in the techniques of stereotactic and functional surgery, who have been trained in the performance of DBS procedures and who have been credentialed by their institutions as competent to perform these procedures. The use of microelectrode recording or macroelectrode stimulation are considered clinically accepted methods for physiological confirmation of the target site. In cases where microelectrode recording is performed, the assistance of a neurologist or neurophysiologist may help to facilitate decisions on a final target and optimize outcomes. However, an appropriately trained neurosurgeon who is skilled in the performance and interpretation of microelectrode recording may not require intraoperative assistance in this area. Interpretation of intraoperative neurophysiological data can thus be performed either by a qualified neurologist or neurosurgeon.

It has been recommended that centers performing DBS should be equipped for functional stereotactic procedures, with the availability of high-resolution scanners, navigational equipment, and electrophysiological monitoring equipment. Optimal outcomes can be achieved by physicians well experienced in the pathology and treatment of movement disorders, stereotactic neurosurgery, and electrophysiology."